

Unexpected reduction of the nitro group in (3-nitrophenyl)-1,2,4-triazines during their aza-Diels–Alder reaction with 1-morpholinocyclopentene

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Unexpected reduction of the nitro group to the amino one during aza-Diels–Alder reaction between (3-nitrophenyl)-1,2,4-triazines and 1-morpholinocyclopentene (neat, 200 °C, argon) occurred to furnish 4-(3-aminophenyl)-6,7-dihydro-5H-cyclopenta[*c*]pyridines.

Aminophenyl-containing pyridines are of interest for their further functionalization leading to new heterocyclic systems.¹ Moreover, they possess biological activity.²

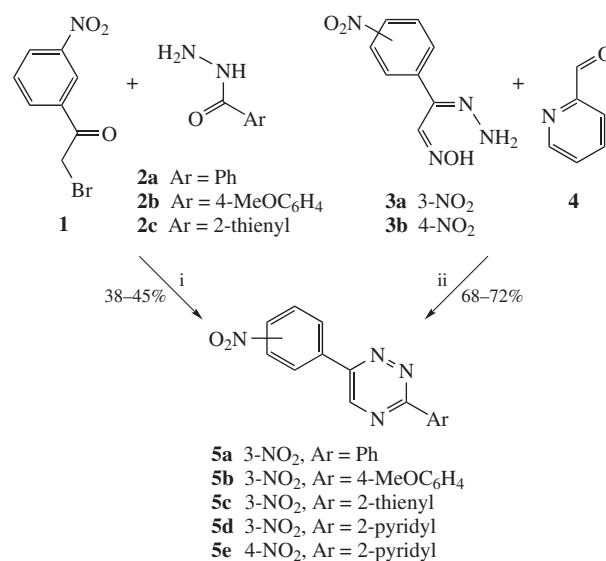
On the other hand, 2-(het)arylpyridines are common ligands for various metal cations, some of them having found use as phosphorescent labels for bioimaging.³ Aminoaryl-substituted derivatives of 2-(het)arylpyridines are good substrates for this purpose, as they can be readily converted into isothiocyanate ones by treatment with thiophosgene just before the bioconjugation.⁴ For the effective bioimaging these functional groups are usually separated from the metal chelating site, *e.g.*, by aromatic substituent(s).

A number of methods for the synthesis of aminophenylpyridines are described in literature.^{5,6} However, only one example based on 1,2,4-triazine methodology for the synthesis of aminophenyl-containing pyridine⁷ is described, although this approach has been recognized as a prospective tool to access various pyridines.⁸ The key advantage of this methodology is the possibility for one-step derivatization of C3 and/or C4 positions in newly formed pyridine ring simply by varying the dienophile and/or the substitution pattern in the starting 1,2,4-triazines. Herein, we describe an application of this methodology to access aminophenyl-containing pyridines.

2-(Het)arylpyridines bearing aminophenyl substituent at C5 position were the targets of our study since cyclometalated complexes of similar ligands possess an intriguing photophysical properties,⁹ therefore these complexes can be promising chromophores for the photoluminescent imaging of biomolecules. In addition, the phosphorescent label based on platinum complex of similar ligand containing carboxylic group for further conjugation with biomolecule was reported.¹⁰

For the synthesis of parent 1,2,4-triazines two previously described methods were used.¹¹ Interaction of 2-bromo-3'-nitroacetophenone **1** with two equivalents of carboxhydrazides **2** or condensation of isonitrosoacetophenone hydrazones **3** with pyridine-2-carboxaldehyde **4** afforded triazines **5a–e** (Scheme 1, for details, see Online Supplementary Materials).

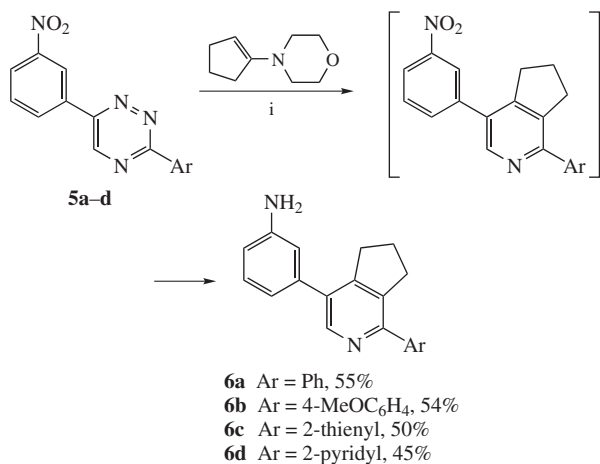
Comparative studies of photophysical properties of platinum complexes of 5-aryl-2-(2-thienyl)pyridines and the corresponding cyclopenteno[*c*]pyridines demonstrated that the latter exhibit higher values for both the luminescence lifetime and quantum yield,^{9(a)} therefore they are more preferable for application as phosphorescent labels for bioimaging. To obtain cyclopenteno[*c*]pyridines from 1,2,4-triazines **5**, 1-morpholinocyclopentene should be used as the dienophile in the aza-Diels–Alder reaction.



Scheme 1 Reagents and conditions: i, AcONa, EtOH–AcOH (3:1), 105 °C, 12 h; ii, ethanol, 20 °C, 10 h, then AcOH, 118 °C, 5 min.

The target cyclopenteno[*c*]pyridines **6** were prepared as described¹² by heating 1,2,4-triazines **5a–d** with an excess of enamine at 200 °C without solvent under argon atmosphere. Unexpectedly, the processing not only led to the complete formation of the cyclopentenopyridine system, but also caused the reduction of nitro group into the amino one (Scheme 2).[†] It should be noted that for the full conversion of **5**, longer reaction time compared to the original procedure was required.

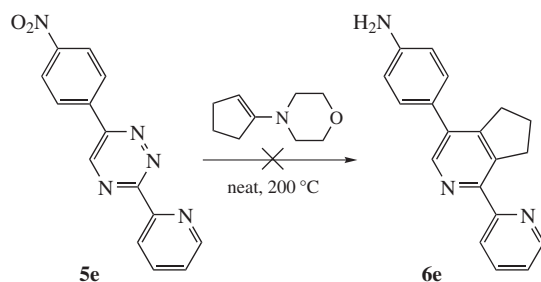
[†] Synthesis of 6,7-dihydro-5H-cyclopenteno[*c*]pyridines **6**, **9** and **10** (typical procedure). Mixture of corresponding triazine **5**, **7** or **8** (2 mmol) and 1-morpholinocyclopentene (1.6 ml, 10 mmol) was stirred at 200 °C under argon atmosphere for 2 h, after that two more portions of enamine (2×0.64 ml, 2×4 mmol) were added and the reaction mixture was stirred at 200 °C for 1 h after each portion. The mixture was cooled to room temperature and placed as is on chromatographic column (SiO₂) and eluted with chloroform. Combined fractions containing product (*R*_f = 0.2) were concentrated under reduced pressure to *ca.* 10 ml. The product was extracted with 3 N hydrochloric acid (3×20 ml). Sodium hydroxide pellets were added to hydrochloric acid extract upon cooling to adjust pH to 12 and the product was extracted with dichloromethane (3×20 ml). The combined organic extracts were dried with anhydrous sodium sulfate, filtered and solvent was removed under reduced pressure. Analytical sample was recrystallized from ethanol.



Scheme 2 Conditions: i, neat, 200 °C, argon atmosphere, 4 h.

Structures of products **6** were proved by ¹H and ¹³C NMR data (a significant upfield shift of signals of hydrogen atoms of phenyl ring was observed). The presence of amino group in compounds **6** was confirmed by 2D COSY (¹H–¹⁵N) experiment carried out for product **6c**. Thus, the interaction between nitrogen atom (54 ppm) and hydrogen atoms (3.78 ppm) was observed in 2D COSY (¹H–¹⁵N) spectra.

Interestingly, isomeric 4-nitrophenyl-1,2,4-triazine **5e** gave neither nitro- nor aminophenyl-substituted cyclopenteno[c]pyridine **6e** and only a complex mixture of unidentified products was formed (Scheme 3).

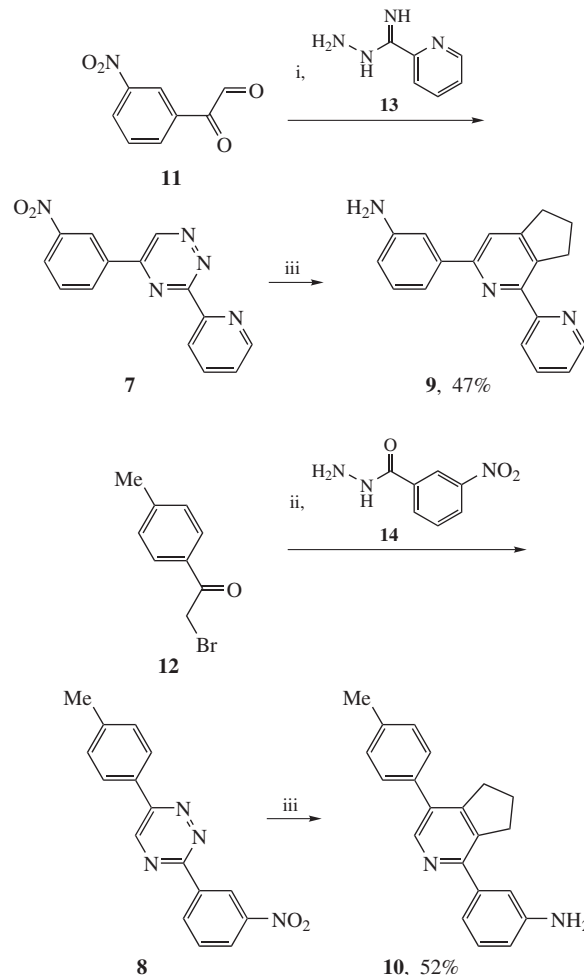


Scheme 3

4-(3-Aminophenyl)-1-phenyl-6,7-dihydro-5H-cyclopenteno[c]pyridine 6a. Yield 315 mg (1.1 mmol, 55%), mp 144–146 °C. ¹H NMR (CDCl₃) δ: 2.08 (m, 2H, 6-CH₂), 3.06 (t, 2H, 7-CH₂, ³J 7.2 Hz), 3.17 (t, 2H, 5-CH₂, ³J 7.2 Hz), 3.78 (br. s, 2H, NH₂), 6.73 [m, 1H, H-4 (3-NH₂Ph)], 6.80 [dd, 1H, H-2 (3-NH₂Ph), ³J 1.8 Hz], 6.89 [m, 1H, H-6 (3-NH₂Ph)], 7.26 [dd, 1H, H-5 (3-NH₂Ph), ³J 8.0 Hz], 7.41 (m, 1H, Ph), 7.48 (m, 2H, Ph), 7.79 (m, 2H, Ph), 8.54 (s, 1H, H-3). ¹³C NMR (CDCl₃) δ: 25.9, 33.0, 33.1, 114.4, 115.1, 119.0, 128.2, 128.3, 128.5, 129.5, 132.8, 137.4, 139.0, 140.1, 146.7, 147.1, 152.5, 152.8. ESI-MS, *m/z*: 287.16 (M+H)⁺ (required 287.15). Found (%): C, 83.60; H, 6.27; N, 9.69. Calc. for C₂₀H₁₈N₂ (%): C, 83.88; H, 6.34; N, 9.78.

3-(3-Aminophenyl)-1-(2-pyridyl)-6,7-dihydro-5H-cyclopenteno[c]pyridine 9. Yield 270 mg (0.94 mmol, 47%), mp 108–110 °C. ¹H NMR (CDCl₃) δ: 2.13 (m, 2H, 6-CH₂), 3.00 (t, 2H, 7-CH₂, ³J 7.6 Hz), 3.45 (t, 2H, 5-CH₂, ³J 7.2 Hz), 3.75 (br. s, 2H, NH₂), 6.73 [m, 1H, H-4 (3-NH₂Ph)], 7.26 [m, 2H, H-5 (3-NH₂Ph), H-5 (Py)], 7.45 [m, 1H, H-6 (3-NH₂Ph)], 7.51 [dd, 1H, H-2 (3-NH₂Ph), ³J 2.0 Hz], 7.63 (s, 1H, H-4), 7.81 [ddd, 1H, H-4 (Py), ³J 7.8, 7.8 and 2.0 Hz], 8.43 [dd, 1H, H-3 (Py), ³J 7.8 and 1.0 Hz], 8.69 [dd, 1H, H-6 (Py), ³J 4.8 and 2.0 Hz]. ¹³C NMR (CDCl₃) δ: 25.1, 32.8, 33.0, 113.8, 115.4, 116.6, 117.3, 122.7, 123.2, 129.5, 136.3, 138.0, 141.0, 146.8, 148.4, 151.2, 154.6, 156.7, 158.8. ESI-MS, *m/z*: 288.15 (M+H)⁺ (required 288.15). Found (%): C, 79.22; H, 5.80; N, 14.72. Calc. for C₁₉H₁₇N₃ (%): C, 79.41; H, 5.96; N, 14.62.

For synthesis of compounds **5**, **7** and **8** and characteristics of compounds **6b–d**, **7**, **8** and **10**, see Online Supplementary Materials.



Scheme 4 Reagents and conditions: i, ethanol, 78 °C, 2 h; ii, ethanol–AcOH (3:1), 90 °C, argon atmosphere, 10 h; iii, 1-morpholinocyclopentene, neat, 200 °C, argon atmosphere, 4 h.

In order to investigate the influence of the position of 3-nitrophenyl substituent onto the reaction outcome we tested other 3-nitrophenyl-substituted 1,2,4-triazines^{11(a),13} **7** and **8**, which gave amino pyridines **9** and **10** in satisfactory yields (Scheme 4).[†]

Presumably enamine acts as a reducing agent in this transformation, with the inert atmosphere being an essential factor. Mechanism of the reaction is under study. Some literature data¹⁴ support our hypothesis, *i.e.* the reaction of 2,6-bis[6-(4-nitrophenyl)-1,2,4-triazin-3-yl]pyridine with excess of enamine in boiling 1,4-dioxane in air occurred only as a 1,2,4-triazine-to-pyridine transformation with nitro group remaining untouched. Refluxing of nitrobenzenes in neat 1-pyrrolidinocyclohexene (more powerful reducing agent) caused the complete reduction of the nitro group. Position of the nitro group in the aromatic substituent in 1,2,4-triazine system is also important. In particular, in case of 4-nitrophenyl-1,2,4-triazines (*e.g.*, **5e**) no 4-aminophenylpyridines were isolated. Such a low reactivity can be explained by the conjugation between nitro group and 1,2,4-triazine system as an electron-withdrawing substituent. Apparently, in case of 3-nitrophenyl substituent conjugation between nitro group and 1,2,4-triazine core is weaker.

In conclusion, we have suggested a good method for the conversion of 3-nitrophenyl-substituted 1,2,4-triazines into aryl-6,7-dihydro-5H-cyclopenteno[c]pyridines **6a–d**, **9**, **10** bearing 3-aminophenyl moiety, which seems promising for their further conjugation with biomolecules. This method is advantageous in view of the little number of steps and simplicity of the processing.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2013.07.010.

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